Mechanisms of small RNA regulation in early embryonic development

Grant Award Details

Mechanisms of small RNA regulation in early embryonic development

Grant Type: New Faculty II

Grant Number: RN2-00906

Project Objective: To understand the role of small RNAs in stem cells and early development.

Investigator:

Name:	Robert Blelloch
Institution:	University of California, San Francisco
Type:	PI

Human Stem Cell Use: Embryonic Stem Cell

Award Value: $2,790,695

Status: Closed

Progress Reports

Reporting Period: Year 1

View Report

Reporting Period: Year 2

View Report

Reporting Period: Year 3

View Report

Reporting Period: Year 4

View Report

Reporting Period: Year 5

View Report

Reporting Period: NCE

View Report

Grant Application Details

Application Title: Mechanisms of small RNA regulation in early embryonic development

Public Abstract: The promise of embryonic stem cells in regenerative medicine is based on their potential to make every cell in the body, a property coined pluripotency. With rapid recent advances in technology, it is becoming relative straightforward to make embryonic stem cell-like lines from adult tissues. In the near future, the generation of these lines will become increasingly common practice including the production of patient-specific lines that can be used to evaluate the disease and even replace damaged tissue in these patients. However, we still do not fully understand the molecules that underlie pluripotency. It is essential for us to do so, in order to improve on the generation and quality control testing of the embryonic stem cells. Exciting recent work has shown that modifications to the genome that do not change the actual DNA sequence, but do change how that sequence is presented, is a central component of pluripotency. These modifications have been coined epigenetic modifications because they are not altering the underlying genetic code. Specifically, it was recently shown that these epigenetic modifications maintain the stem cell's capacity to proliferate while poising them to differentiate into all tissues of body. They do so by keeping the programs required for differentiation into adult tissues off, but still accessible to activation. Failure in establishment and/or maintenance of the correct epigenetic program leads to diminished pluripotency and even tumor risk. Unfortunately, very little is known about how the epigenetic program of embryonic stem cells is established and maintained. This grant proposes that a novel class of regulators called small RNAs is essential for the establishment and maintenance of epigenetic program underlying pluripotency. To test this proposition, the investigators intend to use tools that enable them to remove different subtypes of small RNAs. They will test the effects of the removal of these RNAs on the establishment and maintenance of the epigenetic program underlying pluripotency. Furthermore, they will identify the molecular nature of these small RNAs and evaluate how individual small RNAs influence these epigenetic modifications. Once the critical small RNAs are identified and their specific functions uncovered it should be possible to use these small RNAs both to improve the efficiency of derivation of quality embryonic stem cell lines as well as potentially even fix damaged embryonic stem cell lines, in particular lines that have lost some aspects of their potential to differentiate into adult tissues.

Statement of Benefit to California:	This grant proposes to uncover mechanisms that are central to providing embryonic stem cells with their amazing potential to produce all the cell types of the body. This potential makes embryonic stem cells a powerful tool for both evaluating and treating disease. For example, it is now becoming increasingly clear that soon it will be possible to produce patient specific embryonic stem cells that can then be differentiated into any tissue(s) of choice including those responsible for a patient's specific ailment. The resulting tissue can then be analyzed for the unique causes of the patient's disease and even evaluated for responsiveness to a panel of drugs. This personalized treatment of disease will have broad positive impacts in how health care is delivered as it will take in account the differences between every patient's specific ailment and response to treatment. However, before this approach can be put into clinical practice in the most efficient way, there remains a lot to be learned about embryonic stem cells themselves. That is, what provides them with their amazing potential? This is the question addressed by this grant proposal. In particular, the grant proposes to uncover mechanisms central to determining and maintaining the potential of embryonic stem cells. Uncovering such mechanisms will allow the medical and pharmaceutical community to improve the efficiency at which they can produce embryonic stem cell lines as well as quality control the resulting cells. It could even enable the correction of defects in a particular stem cell line's potential. The little we already have learned about the mechanisms underlying a embryonic stem cell's developmental potential has lead to major practical advances including the recent success of producing human embryonic stem cells from adult skin cells. This will be the tip of iceberg. The more mechanisms we uncover, the more sophisticated the manipulations we will be able to perform and the more profound the therapeutic possibilities. Therefore, completion of this proposal should have positive health and financial impacts for the state of California.